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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/607,455	BATES ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 17-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 10-16, 40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/15/04; 2/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-41 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-6, 10-16, 40 and 41 drawn to a method of detecting apoptosis by detecting at least one of nucleolin and PARP-1 in the sample using anti-nucleolin antibody and anti-PAPR-1 antibody, filed 10/3/05, is acknowledged. The traversal is on the grounds that the office fails to provide any discussion about the reasons for restricting between Groups 1 and 2 where group 2 is drawn to a method of detecting apoptosis using oligonucleotide. This is not found persuasive because of the reasons set forth in the restriction mailed 6/29/05. As is well known in the art, oligonucleotide binds to other nucleotide. Antibodies are proteins that bind to other proteins. The two types of molecules therefore have different functions – binding to nucleotide versus binding to other proteins, different modes of operation – nucleotide-nucleotide interactions versus protein-protein interactions. Reasons as to why the two groups are distinct are also provided in the previous office action (see page 3, paragraph 8). A product is distinct from a process of use if it has other uses. Methods are different if they have different method steps, goals, or outcome measures. Thus, as was stated in the previous office action, they differ structurally and functionally and cannot be used together or interchangeably. A search of antibody in the protein databases will not encompass the oligonucleotide in the nucleic acid databases and vice versa. A prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group 1 and Groups 2-8 is still deemed proper and is therefore made FINAL.

3. Claims 7-9 and 17-39 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-6, 10-16, 40 and 41, drawn to a method of detecting apoptosis by detecting at least one of nucleolin and PARP-I in the sample using anti-nucleolin antibody and anti-PAPR-I antibody, are being acted upon in this Office Action.

5. The drawings, filed 6/26/03, are not approved because the back ground of Figures 1 and 2 are too dark. Appropriate action is required.

6. The disclosure is objected to because of the following informality: Table 1A on page 13 needs to be filled in. Correction is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6, 10-16, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of detecting apoptosis comprising the steps of preparing a cell sample, disrupting the cell membrane, and detecting nucleolin and PARP-1 with an antibody that binds specifically to nucleolin (110 KD) and an antibody that binds specifically to poly(ADP-ribose) polymerase-1 PARP-1 (89 KD) wherein apoptosis is detected with an increase in PARP-1 (89 KD) and a decrease in nucleolin (110 KD), (2) the said method wherein the sample is from blood, serum, plasma, tissue, tissue culture medium or sputum, (3) the said method wherein the anti-nucleolin antibody detects nucleolin or nucleolin-PAPR-1 complex, (4) the said method wherein the anti-PARP-1 antibody detects PARP-1 or PARP-1-nucleolin complex, (5) a method of detecting excessive apoptosis in a subject, comprising preparing a blood sample from which cells have been removed from the subject, and detecting nucleolin and PARP-1 in the sample with an antibody that binds specifically to nucleolin (110 KD) and an antibody that binds specifically to PARP-1 (89 KD) wherein apoptosis is detected with an increase in PARP-1 (89 KD) and a decrease in nucleolin (110 KD), (6) the method of detecting excessive apoptosis in a subject wherein the subject is suspected of having a disease selected from the group consisting of Acquired Immunodeficiency Syndrome, a neurodegenerative disease, an ischemia injury, an autoimmune disease, cancer, viral infection, an acute inflammatory condition and sepsis, (7) the method of detecting excessive apoptosis in a subject wherein the subject is suspected of having cancer wherein the cancer is selected from the group consisting of endocervical adenocarcinoma, prostatic carcinoma, breast cancer, leukemia, and non-small cell lung carcinoma, (8) a method of detecting apoptosis in a cell culture comprising the steps of preparing a cell sample, disrupting the cell membrane, and detecting nucleolin and PARP-1 with an antibody that binds specifically to nucleolin (110 KD) and an antibody that binds specifically to PARP-1 (89 KD) wherein apoptosis is detected with an increase in PARP-1 (89 KD) and a decrease in nucleolin (110 KD), and (9) the method of detecting apoptosis in a cell culture

wherein the cell culture is grown in a bioreactor, **does not** reasonably provide enablement for a method of detecting apoptosis as set forth in claims 1-6, 10-16, 40 and 41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of detecting apoptosis comprising the steps of preparing a cell sample from UV irradiated or camptothecin or topoisomerase inhibitor treated U937 cells, disrupting the cell membrane, detecting nucleolin and PARP-1 with an antibody that binds specifically to nucleolin (110 KD) and an antibody that binds specifically to PARP-1 (89 KD) wherein apoptosis is detected with an *increase* in PARP-1 (89 KD) and a *decrease* in nucleolin (110 KD) (page 34-35).

The specification does not teach how to make any compound for use in detection of apoptosis by detecting any nucleolin and any PARP-1 because the chemical structure and/or amino acid sequence of the undisclosed compound/ agent is required. There is insufficient guidance and objective evidence as to how to make and to how to use any agent, in turn, would be useful for detecting apoptosis. There is insufficient guidance to direct a person of skill in the art to select particular sequences as essential for making agent or compound that binds specifically to any and all nucleolins, any agent or compound that binds specifically to any PARP-1 for detecting apoptosis. A person of skill in the art could not predict which particular amino acid sequences are essential and could be used for detecting apoptosis.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Even if the method of detecting apoptosis is limited to the use of antibody that binds specifically nucleolin and the antibody that binds specifically to PARP-1, apoptosis is only

detected with a *decrease* in nucleolin (110 kD band) and a concomitant *increase* in the PARP-1 fragment (89 kD), not the full length of PAPR-1 (118kD). This is because PARP-1 is cleaved by caspase-3 from a full length PARP-1 (118 kD) to PARP-1 (89 kD) (see page 35 of specification). Detecting the full length PARP-1 does not indicate that apoptosis had occurred. Therefore, only the cleaved product of PARP-1 (89 kD), not the full-length is associated with apoptosis. Further, the specification as file does not teach how to make any and all antibodies that bind to any PARP-1 and any and all nucleolin because the structure of immunogen used for making such antibody have not been described and enabled. The term "at least one nucleolin" in claim 1 suggests that there are more than one nucleolins. The specification as filed discloses only one nucleolin described by Bandman et al (page 2), much less antibodies that bind to more than one nucleolin, let alone the other undisclosed nucleolins are also involved in apoptosis. There is insufficient guidance and objective evidence as how to make and to how to use any agent and/or antibodies that bind to one or more nucleolin, in turn, would be useful for detecting apoptosis. There is insufficient guidance to direct a person of skill in the art to select particular sequences as essential for making antibody that binds specifically to any and/or all nucleolins. There is also insufficient guidance as to the binding specificity of all antibodies that bind to any nucleolins and/or PARP-1. A person of skill in the art could not predict which particular amino acid sequences of which nucleolins and PARP-1 are essential and could be used for making antibody that binds specifically to nucleolin or PAPR-1, and could be used for detecting apoptosis as broadly as claimed. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds can result in substantially different binding specificity.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Since the binding specificity of the antibody for the claimed method are not enabled, it follows that the methods of detecting apoptosis using any agent, any antibody are not enabled.

With regard to claim 6 and 12, it is not clear that the anti-nucleolin antibodies "p7-14A, sc-8031, sc-9893, sc-9892, 4E2 and 3G4B2" recited in claim 6 and the anti-PARP-1 antibodies "sc-1562, sc-8007, sc-1561, sc1561-Y and sc-7150" recited in claim 12 for the claimed method are exactly the same antibodies as indicated in the various commercial catalogs from Developmental Studies Hybridoma Bank, MBL International, Upstate, and Santa Cruz Biotech disclosed on page 12-13 of the specification. Further, it is noted that antibody such as sc-9892 and sc1561-Y are no longer commercially available to the public. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 1-6, 10-16, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any antibody that binds to "at least one nucleolin" and (2) any antibody that binds to "PARP-1" for the methods of detecting apoptosis.

The specification discloses only a method of detecting apoptosis comprising the steps of preparing a cell sample from UV irradiated or camptothecin or topoisomerase inhibitor treated U937 cells, disrupting the cell membrane, detecting nucleolin and PARP-1 with an antibody that binds specifically to nucleolin (110 KD) and an antibody that binds specifically to PARP-1 (89 KD) wherein apoptosis is detected with an *increase* in PARP-1 (89 KD) and a *decrease* in nucleolin (110 KD) (page 34-35).

The specification does not adequately describe any agent, any compound for use in detection of apoptosis by detecting any nucleolin and any PARP-1 because the chemical structure

and/or amino acid sequence of the undisclosed agent or compound is required to detect apoptosis. There is insufficient written description about the structure associated with function of any agent, any compound for detecting apoptosis other than the specific antibodies that bind to nucleolin (110 KD) and an antibody that binds specifically to PARP-1 (89 KD).

Even if the method of detecting apoptosis is limited to the use of antibody that binds specifically nucleolin, and the antibody that binds specifically to PARP-1, apoptosis is only detected with a *decrease* in nucleolin (110 kD band) and a concomitant *increase* in the PARP-1 fragment (89 kD), not the full-length of PAPR-1 (118kD) or any PARP-1 as claimed. This is because PARP-1 is cleaved by caspase-3 from a full length PARP-1 (118 kD) to PARP-1 (89 kD) (see page 35 of specification). Therefore, only the cleaved product of PARP-1 (89 kD), not the full-length is associated with apoptosis.

Further, the term "at least one nucleolin" in claim 1 suggests that there are more than one nucleolins. The specification as filed discloses only one nucleolin described by Bandman et al (page 2), the structure of other nucleolins to which the antibody binds in the claimed method is not adequately described.

With regard to "nucleolin binding molecule-nucleolin complex" in claim 4 and "PARP-1 binding molecule-PARP-1 complex" in claim 10, the specification discloses only PARP-1-nucleolin complex detected by PARP-1 antibody and nucleolin antibody on the immunoblot, the other "nucleolin binding molecule" in the "nucleolin binding molecule-nucleolin complex" or the other "PARP-1 molecule" in the "PARP-1 binding molecule-PARP-1 complex" are not adequately described.

The specification discloses only antibody that binds specifically to nucleolin (110 kD), PARP-1 (89 kD) for the method of detecting apoptosis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of agent, compound and/or antibody that binds to other nucleolins, other PARP-1, other "nucleolin binding molecule-nucleolin complex", and "PARP-1 binding molecule-PARP-1 complex" to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 1 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "PARP-1" in claims 1 and 13 is indefinite and ambiguous because while abbreviation can be used in a claim, to avoid potential confusion, the first recitation of the abbreviation should be preceded by the full terminology, such as poly(ADP-ribose)polymerase (PARP-1), for example.

12. Claims 1-4, 10, 13-16, 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements in the claimed method, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements in claims 1 and 13 are: the specific antibodies that bind to the specific nucleolin (110 kD) and PARP-1 (89 kD).

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-5, 10-11, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Martelli et al (J cellular Biochemistry 78: 264-277, 2000; PTO 892).

Martelli et al teach a method of detecting apoptosis comprising preparing a sample from which cells such as HL60 have been removed from tissue culture (see page 265, col. 1, Materials and methods, Cell Culture and Induction of Apoptosis, in particular), detecting nucleolin using monoclonal antibody that binds to protein C23/nucleolin and monoclonal antibody such as C-2-10 that binds to PARP from Oncogene Research Products (see page 265, paragraph bridging col. 1 and col. 2, page 269, col. 2, fourth paragraph, Figure 7, in particular). Martelli et al further teach the method further comprises membrane disruption by lysing the cells in lysis buffer (see page 266, col. 1, Polyacrylamide Gel Electrophoresis and Immunobloting of Cell Lysates, page 275, Figure 9, in particular). Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 2, and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martelli et al (J cellular Biochemistry 78: 264-277, 2000; PTO 892) in view of US Pat 6,350,452 B1 (filed Dec 8, 1999; PTO 892).

The teachings of Martelli et al have been discussed supra. Martelli et al further teach apoptosis can be detected using antibody that binds to protein C23/nucleolin and antibody such as C-2-10 that binds to PARP and the increase rate of apoptosis are responsible for various disease such as degenerative disease, autoimmune disease, and carcinoma (see page 264, col. 1, in particular).

The claimed invention in claim 2 differs from the teachings of the reference only in that the method of detecting apoptosis wherein the sample is from blood, serum, plasma or sputum.

The claimed invention in claim 13 differs from the teachings of the reference only in that the method of detecting apoptosis in a subject by preparing a blood sample from which cells have been removed and detecting at least one of nucleolin and PARP-1 in the sample instead of cells taken from tissue culture.

The claimed invention in claim 14 differs from the teachings of the reference only in that the method of detecting apoptosis in a subject wherein the subject having a disease selected from neurodegenerative disease, an ischemic injury, an autoimmune disease, a tumor or cancer.

The claimed invention in claim 15 differs from the teachings of the reference only in that the method of detecting apoptosis in a subject wherein the subject having cancer.

The claimed invention in claim 16 differs from the teachings of the reference only in that the method of detecting apoptosis in a subject wherein the subject having cancer wherein the cancer is endocervical adenocarcinoma, prostatic carcinoma, breast cancer, leukemia, or non-small cell lung carcinoma.

The '452 patent teaches a method of detecting apoptosis using various antibodies that binds specifically to PARP-1 in sample taken from a subject having various diseases such as cancer, leukemia, neurodegenerative diseases, autoimmune diseases, heart disease (ischemia) and others (see entire document, abstract, col. 2, lines 46-51, in particular). The reference biological sample is cell or cells collected from biopsy, biological fluid, tissue samples, or cells grown in culture such as HL60 (see col. 4, lines 1-28, in particular). The '452 patent teaches the reference anti-PARP-1 antibody is able to distinguished cleaved and uncleaved PARP-1 in cells undergo apoptosis versus non-apoptotic cells in biological sample obtained from subject having various disease; the reference method of detecting apoptosis provides a better understanding of these diseases and will be useful for screening potential therapeutic agents that may be induce or prevent apoptosis (see col. 3, lines 38-43, col. 45-54, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cell sample taken from tissue culture as taught by Martelli et al for the biological sample collected from a subject having various diseases such as cancer, leukemia, neurodegenerative diseases, autoimmune diseases, heart disease (ischemia) and others for a method of detecting apoptosis in a subject as taught by the '542 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '452 patent teaches detecting apoptosis from a biological sample taken from patient with various diseases such as cancer leukemia, neurodegenerative diseases, autoimmune diseases, heart disease (ischemia) or others will provide a better understanding of these diseases and also be useful for screening potential therapeutic agents that may be induce or prevent apoptosis (see col. 3, lines 38-43, col. 45-54, in particular). Martelli et al teach apoptosis can be detected using antibody that binds to protein C23/nucleolin and antibody such as C-2-10 that binds to PARP and

the increase rate of apoptosis are responsible for various disease such as degenerative disease, autoimmune disease, and carcinoma (see page 264, col. 1, in particular).

18. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Martelli et al (J cellular Biochemistry 78: 264-277, 2000; PTO 892) in view of US Pat 6,096,532 (Aug 2000; PTO 892).

The teachings of Martelli et al have been discussed supra.

The claimed invention in claim 41 differs from the teachings of the reference only in that the method of detecting apoptosis wherein the cell culture is grown in a bioreactor.

The '532 patent teaches a method of growing cell in a bioreactor (see entire document, summary of invention, in particular). The advantages of growing cell in a bioreactor are minimizing the economies of labor, minimizing potential for contamination and optimizing designed for use with a homogenous cell mixture and without exposing the sterile system to the external environment (see col. 7, lines 41-58 bridging col. 8, lines 1-24, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cell sample that were grown in tissue culture for a method of detecting apoptosis as taught by Martelli et al for any cell that are growing in a bioreactor as taught by the '532 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '532 patent teaches the advantages of growing cell in a bioreactor are minimizing the economies of labor, minimizing potential for contamination and optimizing designed for use with a homogenous cell mixture and without exposing the sterile system to the external environment (see col. 7, lines 41-58 bridging col. 8, lines 1-24, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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